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EXAMINER

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1612

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

The amendment dated 8-25-08 is acknowledged.

Claims included in the prosecution are 1-19 and 21-38.

Upon consideration, the 103 rejection of claims over Violanto (4,826,689) in combination with Parikh (5,922,355) and Caza (6,079,508) is withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 8, 9, 11, 17, 18, 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the parent claim 7, the compound is a surface active agent. The dependent claims 8 and 9 recite polysaccharides and various celluloses. It is unclear as to how these compounds can be considered as surfactants. Similar is the case with claims 17 and 18.

'other proteins' in claim 11 and 'other high shear conditions' in claim 23 are indefinite expressions; the examiner suggests reciting specific proteins and specific conditions in these claims.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that polysaccharides and celluloses are amphiphilic and thus properly described as surfactants. It is unclear as to how a polysaccharide such as starch can be

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amphiphilic since it has only functional hydrophilic hydroxyl groups. Applicant has not provided any evidence in support.

Applicant argues that claims are considered definite as long as the scope of the claims is clear. However, such is not the case in this case since the scope of other proteins is unclear. Similar is the case with high shear conditions. High is a relative term. The rejection is maintained.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-7, 11 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,916,596) as set forth in the previous action.

5. Claims 1-9, 11 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,916,596) in view of Popescu (5,009,819).

The teachings of Desai have been discussed before. What is lacking in Desai is the sonication below the room temperature.

Popescu discloses the preparation of submicron size particles of chloroquine. The process involves emulsification of phosphatidylcholine in diethyl ether/chloroform and aqueous chloroquine solution and sonicating the mixture at a temperature of 18 to 20 degrees (example 1).

Sonicating the mixture of Desai at a temperature of 18 to 20 degrees would have been obvious to one of ordinary skill in the art with the expectation of obtaining the best possible results since the reference of Popescu shows that the sonication process could be practiced below the room temperature.

6. Claims 1-9, 11, 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al. US 5916596 in view of Popescu US 6090406 as set forth in the previous action.

7. Claims 1-9, 11, 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al. US 5916596 in view of Popescu US 6090406 as set forth in the previous action, further in view of Popescu (5,009,819).

The teachings of Desai and Popescu (406) have been discussed before. Briefly, Desai teaches the emulsification process using sonication technique to prepare nanoparticulate suspension. Desai however, does not teach that the sonication process is used to remove the organic solvent.

Popescu (406) teaches that the sonication process can be used to remove organic solvent (Example 1). The temperature at which the sonication is carried out however, is above the room temperature.

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Popescu discloses the preparation of submicron size particles of chloroquine. The process involves emulsification of phosphatidylcholine in diethyl ether/chloroform and aqueous chloroquine solution and sonicating the mixture at a temperature of 18 to 20 degrees (example 1).

The use of the sonication to remove the solvent would have been obvious to one of ordinary skill in the art since the reference of Popescu (406) shows that the removal of a solvent by sonication is a routine practice in the art. Sonicating the mixture of Desai at a temperature of 18 to 20 degrees would have been obvious to one of ordinary skill in the art with the expectation of obtaining the best possible results since the reference of Popescu (819) shows that the sonication process could be practiced at a temperature of 18 to 20 degrees.

Applicant's arguments to the above rejections (Desai or Desai in view of Popescu (5,009,819) and/or (6,090,406) have been fully considered, but are not found to be persuasive. Applicant once again argues that US 2003/0096013 which is cited is not available as a reference against pending claims. In response, the examiner **once again** points out that this reference is only cited as interest **and not as reference over which the claims are rejected**. Applicant once again argues that none of the cited documents discloses or suggests, "evaporating essentially all of the water immiscible organic solvent by sonicating the system at a temperature below room temperature. In Desai, applicant argues that sonication is not used to achieve evaporating, as the examiner claimed. According to applicant, Desai explicitly state that "optionally, the organic, and/or aqueous phases are thereafter removed from the mixture after having been

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subjected to high shear conditions. These arguments are not persuasive. First of all, the references do teach the evaporation of the organic solvents by various techniques and as the references cited of interest before by the examiner establish sonication as a technique for the removal of organic solvents. In both prior art and instant cases, the organic solvent is removed and applicant is merely using one of the art known techniques for the removal of organic solvent and has not established any criticality of this technique in the preparation of the product.

Applicant argues that Popescu 819 discloses that the mixture was sonicated at room temperature (18 to 20 C) while concomitantly evaporating the ether with a stream of nitrogen. Applicant argues that Popescu 406 merely discloses sonicating a solution contained in a water bath at 47 C, which corresponds to a temperature in excess of the boiling point of ether and sonication was continued until "substantially all ether" therein was evaporated, but sonication was not performed as claimed because heat was applied to remove the solvent in contrast to the claimed subject matter, which recites "sonicating at a temperature below the room temperature". These arguments are not persuasive. Applicant has not shown any unexpected results by conducting the evaporation below the room temperature. As pointed out before, it would have been obvious to one of ordinary skill in the art to use suitable temperatures depending upon the compound's ability to withstand any particular temperature. As the reference of Orsolini (5,637,568) submitted by applicant indicates that some organic solvents are volatile and solvents such as methylene chloride evaporate spontaneously during agitation (col. 3, lines 17-26). From this fact coupled with the fact that sonicators by

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themselves remove organic solvents, one of ordinary skill in the art would be motivated to use a suitable temperature, a temperature which is below the room temperature if necessary, if the active agent is susceptible to higher temperatures. The examiner has already the reference of Caza (6,079,508) to show that there are some ultrasonic processors, which remove the solvent (see col. 6, lines 9-17). The examiner has also cited Werling (2003/0096013) which shows sonication removes solvent (0059). As also pointed out before, instant claim language 'comprising' does not exclude other evaporation conditions carried out simultaneously and the examiner cited the references of Janoff and Popescu (5,009,819), which teach concurrent evaporation by Nitrogen while sonicating the emulsion of interest (col. 31, lines 25-30 of Janoff; Example 1 of Popescu). Finally, the examiner points out that applicant has not shown any criticality of performing the sonication step to remove the solvent below the room temperature since on page 8, lines 10-12 of the specification, applicants themselves state that any residual solvent that exists may be removed by means such as evaporation by the addition of heat. As discussed above, if the active agent is heat sensitive, one of ordinary skill in the art would select a temperature, which is less than room temperature.

8. Claims 1-19 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Violanto (4,826,689) in combination with Parikh (5,922,355), further in view of Popescu (6,090,406) as set forth in prior action.

Violanto teaches a method of preparing submicronized particles formed by precipitation of the water insoluble compound into an aqueous solution from organic solution (col. 4, lines 32-37). The particle size is in the range 0.5-1.5 microns (col. 3, line

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41). The organic solvent to non-solvent liquid ratio is 1:100 to 100:1 (col. 3, lines 54-56).

The reference further teaches using surfactants such as poloxamer, and suggests that any other surfactant known to those of ordinary skill would be suitable (col. 6, lines 50-55). The reference teaches that the mixture is stirred (col. 5, line 21, col. 6, lines 56-60). What is lacking in Violanto is the teaching of sonicating the mixture at a temperature below room temperature and the removal of the organic solvent.

Parikh discloses a method of preparing submicronized particles of poorly water soluble pharmaceutically active agents comprising reducing the particle size through sonication, homogenization, milling, micro fluidization and precipitation or recrystallization and precipitation of the compound using antisolvent and solvent precipitation techniques (col. 10, lines 23-29). The steps of the method comprise mixing the water insoluble pharmaceutically active ingredient, a phospholipid, with at least one nonionic, anionic, or cationic surfactant and sonicating the mixture at a temperature of 18 degrees (Example 1, col. 10, lines 30-34). Suitable surface-active modifiers used in the invention are listed in column 3, lines 6-30). Parikh's teaches sonicating the composition mixture (col. 4, lines 50-56). A suspension of the particles was made in water (col. 5, 2-3). The particles sizes of the particles were in the range 337-361 nm (col. 5, lines 10-22). Parikh lists types of water insoluble pharmaceutical compounds that would be suitable for this invention (col. 2, lines 52-64). The number weighted particle size range is 63-76 nm (col. 5, lines 20-22).

The use of a sonicator in the process of Violanto would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since the use of

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sonicator for the preparation of submicronized particles of active agents is known in the art as evident from Parikh. Since Violanto teaches a wide range of organic solvent: non-solvent ratios and if the organic solvent is in excess, it would have been obvious to one of ordinary skill in the art to use the sonicator to remove the solvent to such levels as to form the precipitation of the active agent since the reference of Popescu as discussed above teaches that solvents can be removed by sonication (col. 6, lines 9-18).

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Violanto does not suggest the desirability of performing an evaporation step, much less evaporating essentially all of the water immiscible organic solvent by sonicating the system/emulsion at a temperature below room temperature, thereby precipitating particles of a compound as claimed. This argument is not persuasive since Violanto teaches the importance of organic solvent to non-solvent ratios in the precipitation of the compounds and it would have been obvious to one of ordinary skill in the art to use any technique to remove excess organic solvent, if present, to precipitate the compound. Sonication is one of the techniques used to remove organic solvents as evident from the reference of Popescu as discussed already and one of ordinary skill in the art would be motivated further to use sonication, with a reasonable expectation of success since the reference of Parikh shows the use of such a technique for the preparation of submicronized particles of poorly water soluble pharmaceutical agents. As pointed out above, applicant has not shown any unexpected findings resulting from using sonication as opposed to other techniques of the removal of organic solvents such as evaporation using nitrogen.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK